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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,536	12/10/2001	David M. Kranz	103-00	9971

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 01/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,536	KRANZ ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *11-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/29/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on August 18, 2003.

Status of the Claims

2. Claims 1-25 were pending in the present application.

3. Applicant's August 18, 2003 response to the Restriction and/or Election of Species requirements is acknowledged (Applicant elected ***with traverse*** Group I i.e., claims 1-10) and claims 11-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim (see ***Response to Restriction and/or Election of Species*** below).

4. Please note: Applicant's elected species (tag = c-myc; Disease = insulin dependent diabetes mellitus) was found in the art. Furthermore, Applicant's *specifically* elected species (MHC chimeric protein = sci-A^{g7}; mutation = GAD65MUT11;) was searched and was not found in the prior art. Thus, the search was expanded to non-elected species, which *were* found in the prior art, see rejections below. Also, see MPEP § 803.02 (emphasis added):

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be

rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species.*** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

5. Therefore, claims 1-10 are examined on the merits in this action.

Response to Restriction and/or Election of Species

6. Applicant's election of Group I (claims 1-10) **with traverse** in Paper No. 9 is acknowledged.

7. The traversal is on the ground(s) that "the claims of Groups I, II, III, IV, V and VI have, as the heart of the invention, the isolation and characterization of mutagenized MHC Class II chimeric proteins. Accordingly, Applicants respectfully urge that the Examiner rejoin ... because of the relatedness of the subject matter" (see August 18, 2003 response, page 2, middle paragraph).

8. These arguments were fully considered but were not found persuasive. As stated in the Restriction Requirement dated June 1, 2003 (Paper No. 7), these inventions (i.e., Groups I-VI) have acquired a separate status in the art as shown by their different classification and/or divergent subject matter. The Examiner contends that while there may be overlapping subject material, the searches would not be coextensive because there is also non-overlapping subject

material. Consequently, the different methods and/or products would require different searches in both the patent and non-patent databases. Therefore, this does create an undue search burden for the Office. Furthermore, the Examiner notes that Applicants "make no admission that any one group of claims is obvious over any other group of claims" (see August 18, 2003 response, page 2, middle paragraph).

9. Applicant's election of species in the August 18, 2003 response is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election of species has also been treated as an election without traverse (MPEP § 818.03(a) and/ or 37 CFR 1.111(b)).

10. As a result, the restriction requirement and/or election of species is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

11. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

12. The references listed on applicant's PTO-1449 form (May 29, 2003 submission) have been considered by the Examiner. A copy of the form is attached to this Office Action. The Examiner notes that references that have been crossed out by Applicants on the PTO-1449 form have not been considered.

Specification

13. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Objections to the Claims

14. Claim(s) 6-10 are objected to because of the following informalities:

A. Claim(s) 6-10 are objected to under 37 CFR 1.75(c) as being improper form because a multiple dependent claim depends from another multiple dependent claim. See MPEP § 608.01(n). For compact prosecution all disputed claims are treated as dependent on the claim immediately prior if not otherwise specified.

Claim Rejections - 35 USC § 101/112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
>
> The following is a quotation of the first paragraph of 35 U.S.C. 112:
>
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-10 are rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility. The instant application has provided a description of a mutagenized combinatorial library of Major Histocompatibility Complex (MHC) Class II chimeric proteins displayed on the surface of recombinant yeast cells wherein at least one member of the library has improved conformation stability or, alternatively, express a higher level of yeast cell surface display with respect to I-A^{g7}. However, the instant application does not disclose the biological role of any of the "stabilized" library members or their biological significance. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66 No. 4, pages 1092-1099, Friday January 5, 2001.

It is clear from the instant specification that a mutagenized library of MHC class II chimeric proteins has been produced and displayed on the surface of recombinant yeast cells wherein several mutants of said library including β56β57 variants (e.g., $\beta56_{His\rightarrow Glu}$ and $\beta57_{Ser\rightarrow Leu}$) are stabilized with respect to the native I-Ag7 (i.e., $\beta56_{His}$ and $\beta57_{Ser}$). However, Applicants do not provide any evidence showing that these "stabilized" proteins have improved binding capabilities for peptides and/or T cell receptors that play a role in autoimmune diseases including Applicants' preferred insulin dependent diabetes mellitus embodiment (e.g., see claim 8). In fact, Applicants admit in their 2003 Protein Engineering paper (see Starwalt, S. E.;

Masteller, E. L.; Bluestone, J. A.; Kranz, D. M. "Directed evolution of a single-chain class II MHC product by yeast display" Protein Engineering 2003, 16(2), 147-156) that these studies have not yet been performed (e.g., see Starwalt et al, page 155, column 2, paragraphs 2, "It remains to be seen [i.e., these experiments have NOT yet been performed and Applicants do not know if they will work] if it is possible to engineer I-A^{g7} variants in positions 56 and 57 that would bind to both autoimmune peptides and the T cell receptors that are associated with disease pathogenesis") (emphasis added). Furthermore, even if *assuming arguendo* that Applicants could show that any of their claimed mutant library members do bind to peptides that would form stable peptide-MHC class II complexes, Applicants further admit that "[t]here are currently no antibody or high-affinity T cell receptor probes for specific peptide-I-A^{g7} complexes [i.e., there are no probes for Applicants' most preferred embodiment]" that would enable them to establish a biological role for their claimed invention in autoimmune pathogenesis (e.g., see Starwalt et al, page 155, column 2, paragraph 4).

After complete characterization, some of these mutagenized proteins library members (e.g., β56β57 variants) may be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 USPQ 689 (Sup. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to posses anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when the term is given its broadest interpretation. However, the court held that his

broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated bye the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available from-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion.

Here, the instant claims are drawn to a library of mutagenized MHC Class II chimeric proteins that have not been fully characterized and, as a result, have no determined "real world" function or biological significance. Applicants have not provided any evidence that their mutagenized library members including SEQ ID No. 17 (e.g., see claim 10) plays any role whatsoever in pathogenesis (i.e., Applicants have only shown that that these proteins can be displayed on the surface of a yeast cell). Until some actual and specific significance can be attributed to these library members, the instant invention is incomplete. To characterize the binding of Applicants' claimed "stabilized" mutagenized library members for peptides and/or T cell receptors associated with an autoimmune disease is clearly to use Applicants' claimed invention as the object of further research, which has been determining by the courts to be a non-patentable utility. Furthermore, Applicants admit that they are unable to determine the T cell binding properties of the claimed invention and thus unable to establish a biological role or "real world" use for said library members because "[t]here are currently no antibody or high-affinity T cell receptor probes for specific peptide-I-A^{g7} complexes" (see Starwalt et al, page 155, paragraph 4). Since the instant specification does not disclose a "real world" use for this mutant

library, the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 1-10 are also rejected under 35 USC 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, even if *assuming arguendo* the mutagenized library in claims 1-10 did support a specific and substantial utility, Applicants would still NOT be enabled for the full scope of the claimed invention because applicants have admitted in the 2003 Protein Engineering paper (see above) that they are not able to show that these library members have increased peptide binding and/or T cell receptor binding properties (e.g., see Starwalt et al, page 155, paragraphs 2-4 as discussed above). That is, applicants have only shown that the MHC class II mutants can be expressed at higher levels. In addition, Applicants have only shown examples wherein the AGA2 mating adhesion receptor has been employed to attach the library members to the yeast cells and thus would not be enabled for any other adhesion receptor protein.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b)

only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

16. Claims 1-9 are rejected under 35 U.S.C. 102(e) as being anticipated by Zhu et al (WO 02/055718 A2) (Filing Date is **October 31, 2001**) (Priority Date is **October 31, 2000**).

For ***claim 1***, Zhu et al (see entire document) discloses "a library of expression vectors encoding a library of protein complexes, each vector comprising: a first nucleotide sequence encoding a first polypeptide subunit; and a second nucleotide sequence encoding a second polypeptide subunit; wherein the first and second nucleotide sequences each independently varies within the library of expression vectors" (see Zhu et al, claim 1; see also abstract), which anticipates claim 1. For example, Zhu et al discloses that said first and/or said second polypeptide subunits may be subunits of a multimeric protein including MHC Class II proteins (e.g., see page 21, line 10; see also claim 16; see especially page 49, last paragraph, "the variable sequences V1 and V2 of the library of expression vectors may also be derived from multimeric proteins other than antibodies ... e.g., class II MHC; see also page 50, lines 12-17; see also claims 15-16). In addition, Zhu et al discloses displaying the libraries of MHC class II chimeric proteins on the surface of yeast cells (e.g., see claims 2 and 46-47, "[t]he library of claim 1, where the first or second polypeptide subunit further comprises a yeast agglutinin cell wall protein"). Finally, Zhu et al discloses mutagenizing the MHC proteins with a library of variable regions for increasing the specific binding affinity to a target (e.g., see Field of

Invention; see also page 50, lines 12-17; see also page 50, "The Target Proteins and Peptides" section; see also figures).

For ***claims 2-4***, Zhu et al discloses AGA2 (e.g., see claims 46-47).

For ***claim 5***, Zhu et al discloses a wide range of target proteins (e.g., see page 50, "The Target Proteins and Peptides" section).

For ***claim 6***, Zhu et al discloses c-myc (e.g., see page 78, lines 15-21).

For ***claim 7-8***, Zhu et al discloses insulin dependent diabetes mellitus (e.g., see claim 85; see also page 14, line 30; see also, page 49, line 30; see also page 51, line 9; see also page 100, line 6).

For **claim 9**, Zhu et al does not disclose a target having SEQ ID NO: 19, 22 or 24, but Zhu et al does MHC class II molecules expressed on the surface of yeast cells that fall within the scope of Applicants broad claims and, as a result, must have the same binding affinities i.e., ability to bind to SEQ ID NO: 19, 22 or 24. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Contact Information

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D. Epperson, Ph.D. whose telephone number is (703) 308-2423. The examiner can normally be reached on Monday-Friday from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Jon D. Epperson, Ph.D.
January 17, 2005